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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/713,679	11/14/2003	Denise Faustman	00786/428002	2917

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CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
JUEDES, AMY E	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
01/08/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/713,679	FAUSTMAN, DENISE	
	Examiner	Art Unit	
	Amy E. Juedes, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-15,18,20,21 and 56-58* is/are pending in the application.

4a) Of the above claim(s) *58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-15,18,20,21,56 and 57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks, filed 9/17/07 and 10/30/07, are acknowledged.

Claims 1-11, 16-17, 19, and 22-55 have been cancelled.
Claims 12-13, 15, and 20-21 have been amended.
Claims 56-58 have been added.
Claims 12-15, 18, 20-21, and 56-58 are pending.

2. Newly submitted claim 58 is directed to a species of invention that is independent or distinct from the invention originally claimed for the following reasons: Claim 58 is drawn to a distinct species of method comprising measuring a decrease in leukocyte viability in a mammal with a disease, whereas the elected invention involves comparing a decrease in leukocyte viability between a mammal with a disease and a control mammal.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 58 is withdrawn from consideration as being directed to a non-elected species. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 12-15, 18, 20-21, and 56-57 are being acted upon.

3. The rejection of the claims under 35 U.S.C. 112 second paragraph is withdrawn in view of Applicant's amendment to the claims.

4. The rejection of the claims under 35 U.S.C. 112 first paragraph for lack of written description is withdrawn in view of Applicant's amendment to narrow the "compounds" of claim 12 to TNF-alpha, TNF-alpha inducing substances, or TNF-alpha agonists. Additionally, the rejection under 35 U.S.C. 112 first paragraph for lack of written description for the recitation of TNF-alpha receptor antagonists is withdrawn in view of Applicant's amendment to replace the "TFN-alpha receptor" antagonists with "TNF-alpha" agonists. However, Applicant's arguments relevant to the new grounds of rejection will be addressed below.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 12-15, 18, and 20-21 stand rejected, and claims 56-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification provides insufficient evidence that the claimed method would function to diagnose autoimmune disease as broadly claimed.

As set forth previously, The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, *in re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

"The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)" The MPEP further states that physiological activity can be considered inherently unpredictable.

The instant claims are drawn to a method of diagnosing autoimmune disease, or a predisposition to said disease, comprising contacting a blood sample with a compound that decreases leukocyte viability. A diagnosis of autoimmune disease is made by detecting a preferential decrease in the viability of autoimmune leukocytes, compared to those of normal leukocytes. Thus, the asserted mechanism by which the claimed method functions is that leukocytes from patients with autoimmune disease are more susceptible to cell death. However, the instant claims encompass an overly broad method of diagnosing a wide range of different diseases with different etiologies and pathological mechanisms. For example, the claims encompass diagnosing disease ranging from organ specific autoimmune diseases such as diabetes or multiple sclerosis, to immune deficiencies such as primary agammaglobulinemia, or infectious disease such as hepatitis, or even other diverse diseases including chronic fatigue syndrome, pulmonary fibrosis, or alopecia. It is unlikely that a single diagnosis method could

be effective for such a broad range of different diseases. For example, the instant claims encompass diagnosing alopecia by detecting a decrease in leukocyte viability. However, peripheral blood lymphocytes from alopecia patients display increased resistance toward apoptosis compared to healthy controls (see Zoller et al.). Likewise, multiple sclerosis is associated with impaired apoptosis of PBMCs compared to controls (see Macchi et al.). Additionally, PBMCs from patients with rheumatoid arthritis display reduced apoptosis compared with healthy controls (see Szodoray et al. Fig. 2 in particular). Therefore, the instant method that detects a detects a decrease in leukocyte viability would be unlikely to be effective in diagnosing alopecia, multiple sclerosis, or rheumatoid arthritis, which are diseases known to be associated with increased resistance of lymphocytes toward cell death.

Additionally, even though autoimmune diseases such as type I diabetes are known to be associated with an increase in TNF-alpha mediated apoptosis (see Hayashi et al.), the instant claims encompass measuring cell viability after contact with any "compound" or any TNF-alpha receptor agonist. For example, while leukocytes from mice predisposed to diabetes might be more sensitive to TNF-alpha mediated apoptosis, they are resistant to apoptosis induced by cyclophosphamide (see Colucci et al.). Thus, not all compounds that induce cell death will function in a method of diagnosing autoimmune disease. Furthermore, even if the claims are limited to TNF-alpha receptor agonists, this still encompasses compounds that stimulate functionally different receptors. There are two immunologically distinct TNF-alpha receptors (TNFR1 and TNFR2, see Tartaglia et al.). While TNF-alpha might induce enhanced apoptosis of leukocytes from mice predisposed to diabetes (see Hayashi et al.), it is known that antibody agonists of TNFR1 and TNFR2 mediate distinct activities depending on the experimental conditions. For example, anti-TNFR1 antibodies mediate apoptosis in PBMCs from healthy controls, but do not cause increased apoptosis in PBMCs from autoimmune arthritis patients (see Szodoray et al.). In contrast, antibodies specific for TNFR2 do not mediate cytotoxicity, but rather induce proliferation (see Tartaglia et al., Fig. 1 and Fig. 2, in particular). Additionally, neither TNFR1 nor TNFR2 antibodies induce cell death in T cell blasts, although a combination of anti-TNFR1 and anti-TNFR2 antibodies is comparable to TNF-alpha in inducing T cell death (see Sarin et al., page 3717). These studies demonstrate that the effect of a particular TNF-alpha receptor agonists is unpredictable, and depends on the cell subset, activation status, and specificity of the agonists (i.e. TNFR1 vs. TNFR2).

Based on the state of the art, the instant specification must provide a sufficient and enabling disclosure commensurate in scope with the method of the claims. However, the only examples provided by the instant specification involve contacting blood samples of type I diabetic patients with TNF-alpha, followed by measuring T cell viability. This specific example demonstrates that in humans, T cells from type I diabetics exhibit an increase in cell death compared to controls. The specification further demonstrates that in NOD mice predisposed to diabetes, T cells exhibit increased cell death after culture with TNF-alpha compared to controls. However, no examples are provided that demonstrate that the method can function to diagnose any other organ specific autoimmune diseases, much less the wide range of different pathological conditions and diseases encompassed by the claims. Furthermore, no examples are provided that demonstrate that disease can be diagnosed by contacting with other compounds, including antibody agonists of the TNF-alpha receptor. Accordingly, the method as broadly claimed must be considered highly unpredictable. Given said unpredictability, the method of the instant claims must be considered to require undue experimentation.

Applicant's arguments, and the declaration of Inventor Faustman, filed 9/17/07 have been fully considered, but they are not persuasive.

Applicant argues that as long as the specification

discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, the enablement requirement has been met. Applicant further argues that based on the data provided by the instant specification, as well as the data accompanying the Faustman declaration, the full scope of the present claims is enabled.

The instant claims are drawn to a method of diagnosing a wide range of divergent autoimmune diseases comprising measuring a decrease in leukocyte viability from patients with autoimmune disease compared to controls after contact with TNF-alpha, any TNF-alpha inducing substance, or any TNF-alpha agonist. The data in the instant specification demonstrates that leukocytes from subjects with type I diabetes are more susceptible to TNF-alpha mediated cell death. This clearly does not bear a reasonable correlation to a method encompassing diagnosing any autoimmune disease with any TNF-alpha inducing substance or any TNF-alpha agonist. The declaration of Inventor Faustman states that the claimed method has been performed with a variety of TNF-alpha agonists and inducing substances in a variety of autoimmune diseases. However, the data provided appear to be an average of all autoimmune patients tested after contact with a TNF agonist antibody. This average appears to comprise more than 1000 diabetes patients, as well as ~150 patients with other autoimmune diseases such as lupus, Scleroderma, Sjogeren's syndrome, hypothyroidism, multiple sclerosis, Chrohn's disease, and psoriasis). The fact that the vast majority of the patients tested have type 1 diabetes does not allow a reasonable conclusion to be drawn about the effect of the TNF-alpha agonists on other subsets of patients with autoimmune disease (for example, only 6 patients out of more than 1000 patients depicted in the average results have Psoriasis. Furthermore, the data provided do not specify what type of TNF-alpha agonist antibody was used. As noted above, the effect of TNFR1 agonist antibodies vs. TNFR2 agonist antibodies is highly unpredictable.

Additionally, as noted above, the state of the art regarding diagnosing autoimmune disease by measuring leukocyte viability is extremely unpredictable. For example, Zoller et al. (as noted above) teach that lymphocytes from patients with alopecia display increased viability compared to control lymphocytes after culture with anti-CD3 antibodies (i.e. a "TNF-alpha inducing substance", see Fig. 6.). Likewise, Macchi et al. demonstrate that PBMC from multiple sclerosis patients

increased viability compared to control PBMC after culture with PHA (i.e. a TNF-alpha inducing substance, see Fig. 1). Additionally, Szodoray et al. demonstrate that PBMCs from patients with rheumatoid arthritis are not more susceptible to apoptosis than PBMCs from controls after contact with anti-CD3 or anti-TNFR antibodies (i.e. "TNF-alpha agonists", see Fig. 2). Thus, the state of the art indicates that not all autoimmune disease can be diagnosed by measuring a decrease in cell viability compared to controls after contact with any TNF-alpha inducing substance or TNF-alpha agonist. Therefore, based on the state of the art and the lack of working examples, the instant method is not enabled as broadly claimed.

7. The following are new grounds of rejection necessitated by Applicant's amendment.

8. Claims 12-15, 18, and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, there is insufficient written description to demonstrate that applicant was in possession of the claimed genus of "TNF-alpha agonists" or "TNF-alpha inducing substances".

The instant claims are drawn to a method of diagnosing autoimmune disease comprising contacting cells with a "TNF-alpha inducing substance". Thus, the claims might encompass contacting with a virtually unlimited number of structurally different compounds that induce TNF-alpha, including antibodies, nucleic acid molecules, or small molecules. For example, the claims might encompass anti-CD3 antibodies, ConA, PHA, cytokines, viruses, etc. It is clear that the classes of substances encompassed by the claims have no structural similarity. Additionally, the substances might be functionally different (i.e. acting to induce TNF-alpha by binding to distinct cellular receptors). While the specification does disclose on page 6 several examples of substances that can induce TNF-alpha, they are not sufficiently representative of the virtually unlimited number of structurally and functionally different substances encompassed by the claims.

Furthermore, the instant claims encompass employing any

TNF-alpha agonist in the claimed method. This might encompass a broad range of structurally different molecules. For example, the claims encompass agonists that are antibodies, small molecules, natural or mutant ligands, peptides, etc. Furthermore, the TNF-alpha agonists might function to stimulate different TNF-alpha receptors (i.e. TNFR1 or TNFR2) or might act on TNF-alpha itself, enhancing its ability to bind to TNF receptor. Thus, the claims encompass structurally different agonists that might function to stimulate structurally and functionally different receptors. The specification only discloses antibody agonists of TNF-alpha receptor and TNF-alpha. The disclosure of the natural ligand of TNF-alpha receptors and antibody agonists is not representative of the broad range of structurally different agonists encompassed by the claims. Thus, one of skill in the art would conclude that the specification fails to provide adequate written description to demonstrate that Applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F. 3d 1559, 43, USPQ2d 1398.

Applicant argues that the specification on pages 6-7 provides ample written description of TNF-alpha inducing substances and TNF-alpha agonists, including TNF-alpha, sufficient to reasonably convey to one skilled in the art that Applicant was in possession of the claimed invention.

While the specification does disclose on page 6 several examples of substances that can induce TNF-alpha, they are not sufficiently representative of the virtually unlimited number of structurally and functionally different substances encompassed by the claims. Furthermore, the specification only discloses antibody agonists of TNF-alpha receptor, which is not sufficiently representative of the structurally and functionally different "TNF-alpha" agonists encompassed by the claims.

9. Claims 12-15, 18, 20-21, and 56-57 are rejected under 35 U.S.C. 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) A method for diagnosing autoimmune disease comprising contacting a blood sample with a "TNF-alpha agonist" (Claim 12 and dependent claims 13-15, 18, 20).

B) A method wherein a "statistically significant" decrease in leukocyte viability indicates that a mammal has autoimmune disease (Claim 12 and dependent claims 13-15, 18, 20-21 and 56-57).

Applicant indicates that support for the new limitations can be found on page 6 and in Example 2 of the specification. A review of the specification fails to reveal support for the new limitation.

Regarding A), the instant specification discloses on page 6 that the method can employ an agonist of the TNF-alpha receptor. However, a TNF-alpha receptor agonist has a different scope than a "TNF-alpha agonist". For example, a TNF-alpha agonist might encompass a compound that binds to and enhances the stimulatory effect of TNF-alpha itself.

Regarding B), the instant specification discloses measuring a decrease of leukocyte viability. However, the only disclosure of a "statistically significant" decrease is found in the specific examples, which involve measuring TNF-alpha induced T cell death in patients with type I diabetes. This has a much narrower scope than the instant claims, which encompass measuring a "statistically significant" decrease in viability after contact with any TNF-alpha inducing substance or agonist in a sample from a mammal with any autoimmune disease.

10. No claim is allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened

statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, Ph.D. whose telephone number is 571-272-4471. The examiner can normally be reached on 8am - 5pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

12/28/07

G.R. EWOLDT, PH.D.
PRIMARY EXAMINER

Amy E. Juedes, Ph.D.
Patent Examiner
Technology Center 1600